

CASE REPORT

Induced liver injury after high-dose methylprednisolone in a patient with multiple sclerosis

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SUMMARY

A 33-year-old woman with multiple sclerosis, medicated with high doses of methylprednisolone, cyclophosphamide and glatiramer acetate, was referred to our department due to acute liver injury. The laboratory investigation was normal except for weakly positive antinuclear antibodies. Cyclophosphamide and glatiramer acetate were suspended, and intravenous immunoglobulin with maintenance of high doses of methylprednisolone was initiated. The patient developed another episode of acute hepatitis so the immunoglobulin was stopped. After that, she had three more episodes of elevation of liver enzymes with no hepatic insufficiency while medicated only with high doses of methylprednisolone. At this time, liver biopsy showed focal centrilobular hepatocyte necrosis with minimal interface hepatitis. After the high doses of methylprednisolone were suspended, the patient remained asymptomatic, with normal hepatic enzymes. This case emphasises that, although rare, induced liver injury after high doses of methylprednisolone can occur.

consumption, no toxic exposition and no other medications were reported. Laboratory analysis showed total bilirubin of 16 mg/dL (normal 0.3–1.2 mg/dL), direct bilirubin 9.7 mg/dL (normal 0.1–0.5 mg/dL), aspartate aminotransferase (AST) 710 U/L (normal <35 U/L), alanine aminotransferase (ALT) 2308 U/L (normal <45 U/L), γ -glutamyl transferase (GGT) 247 U/L (normal <55 U/L), phosphatase alkaline 92 U/L (normal 40–150 U/L), prothrombin index 36%, factor V 76% and factor VII 17%. Virology for hepatitis B, C and A, herpes simplex virus, Epstein-Barr virus and cytomegalovirus were negative. Serum immunoglobulins were normal and all autoimmunity markers were negative, except for antinuclear antibodies, which were weakly positive (titre of 1:40), with a fine dense granular pattern. Serum ceruloplasmin, ferritin, transferrin saturation and α 1 antitrypsin were negative. The lymphocyte transformation test was negative for cyclophosphamide and glatiramer acetate. Abdominal ultrasound with liver and spleen evaluation was normal. During hospitalisation, all the patient's medications were suspended and she received supportive therapy only. She gradually recovered with analytical improvement on liver enzymes: total bilirubin 2.6 mg/dL, AST 117 U/L, ALT 275 U/L, GGT 115 U/L and phosphatase alkaline 51 U/L. She was discharged with suspension of cyclophosphamide and glatiramer, but she was maintained on high doses of methylprednisolone and started on human normal intravenous immunoglobulin G (IVIG). After 9 months, she once again developed acute hepatitis with hepatic insufficiency. The analytical and imagiological studies were negative and the antinuclear antibodies remained positive with the same titre. A liver biopsy was performed, which showed severe interface hepatitis, and centrilobular hepatocyte necrosis and mild fibrosis, suggesting an autoimmune or drug-induced liver injury aetiology. At this time, the patient suspended all medication (including IVIG) except the high doses of methylprednisolone, and over the following year she developed three more episodes of elevation of liver enzymes (ALT and AST over five times the upper normal limit), but with no hepatic insufficiency. When she was receiving only high doses of methylprednisolone, the liver biopsy was repeated, showing a focal centrilobular hepatocyte necrosis with minimal interface hepatitis and no fibrosis. After a multidisciplinary discussion, it was decided to suspend the high doses of methylprednisolone and initiate natalizumab.

BACKGROUND

Drug-induced liver injury (DILI) is an important cause of acute liver failure with an estimated incidence of 1–10 000 to 1–100 000 treated patients.^{1 2} The clinical manifestation may vary from transitory mild elevation of liver enzymes to fulminant liver failure and death.³ Multiple sclerosis (MS) is a chronic recurrent autoimmune disease of the central nervous system, of unknown aetiology. High doses of intravenous methylprednisolone are useful for its treatment and are also used in the treatment of other autoimmune disorders and even in acute hepatitis.⁴ Although severe liver injury is not mentioned among the possible side effects of methylprednisolone, acute and serious liver injury induced by corticosteroids can occur. It is extremely rare with only a few cases described in the literature.⁵

CASE PRESENTATION

A 33-year-old woman with a diagnosis of severe MS 9 months prior, was referred to our hospital with jaundice that evolved over 4 days, with no other associated signs or symptoms. In the last sixth months, she had been treated for her MS with cyclophosphamide and glatiramer acetate. She had also been treated with high doses of methylprednisolone 1 g/day, with oral maintenance because of the severity of the disease. No ethanol



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OUTCOME AND FOLLOW-UP

After stopping the high doses of methylprednisolone and starting natalizumab, and after 1 year of follow-up, the patient remains asymptomatic with normal liver enzymes.

DISCUSSION

We present a case of severe liver injury induced by high doses of methylprednisolone in a patient with MS. The diagnosis was established by excluding other causes and other medications, and by the relationship between drug administration/hepatic injury and normalisation of liver enzymes after the suspension of methylprednisolone. In the initial episodes, we could not exclude the fact that the other medications might also have contributed to liver damage, however, we were able to assume the normalisation of liver tests after methylprednisolone withdrawal as a positive dechallenge. Liver dysfunction can occur in patients with MS, but most times it is related to drug toxicity. On review of the literature, few cases of liver injury induced by corticosteroids were found.^{5–6} Besides being a rare condition, it has also been under-reported. The clinical presentation varies from subtle elevation of liver enzymes to fulminant hepatitis. Also, the characteristic features on histological examination exhibit a variety of patterns such as steatohepatitis, interface hepatitis and bridging necrosis.^{5–7}

DILI is uncommon but it represents the most frequent cause for drug withdrawal after initial approval and is an important reason for liver transplant.⁸ The mechanism of toxicity is predominantly idiosyncratic, meaning liver injury is unexpected, and it depends on individual susceptibility related to risk factors and genetic polymorphisms. Idiosyncratic lesions can be divided into immunoallergic and metabolic (non-allergic). The immunoallergic reaction occurs due to the interaction of the drug or its metabolites with cells of the immune system, leading to necrosis and apoptosis of hepatocytes. It can be associated with symptoms of hypersensitivity (eg, rash, fever, joint pain). The metabolic reaction occurs because of an aberrant metabolism of the drug leading to local accumulation of toxic metabolites, subsequent oxidative stress and cell necrosis.^{9–10} The exact mechanism responsible for hepatic injury related to methylprednisolone is unknown. Some authors relate the injury with reactivation of HBV infection and others relate it to drug-induced injury linked to the medication excipient.⁵ It is also supposed to be related to the decrease of nuclear factor- κ B activity, where activation leads to tumor necrosis factor- α production that has a protective effect on the liver.¹¹ In cases of chronic use of low doses of methylprednisolone, steatosis and steatohepatitis can occur leading to subtle changes in liver enzymes. In patients with autoimmune diseases, such as MS, concomitant autoimmune hepatitis (AIH) should always be considered since the prevalence of AIH is 0.017% in the general population and it can be 10 times higher in patients with MS.¹² Distinguishing immune-mediated DILI from AIH is difficult since the clinical presentation can be similar and the histological pattern such as centrilobular necrosis is not helpful in distinguishing the two entities.¹³ AIH a chronic, immunologically mediated inflammation of the liver. The aetiology is uncertain but the disease can be triggered in genetically predisposed persons by environmental factors such as viruses, drugs and herbs. In a report on patients with classical features of AIH, about 9% were drug induced and most of the cases (90%) were associated with minocycline and nitrofurantoin.¹⁴

In our case, applying the simplified diagnostic criteria for AIH was neither compatible nor probable for the disease. The histological pattern with focal centrilobular necrosis and liver

enzyme normalisation after the discontinuation of the methylprednisolone was in favour of an immune-induced drug liver injury. Nevertheless, this histological pattern can also be found in the initial forms of AIH and so, although less probable, we could not exclude drug-induced AIH.

In conclusion, DILI caused by high doses of methylprednisolone is rare and the mechanism is not exactly known. In patients with other autoimmune diseases, such as MS, the diagnosis is difficult to establish because immune mediated liver toxicity and AIH have the same immunological background, and therefore show the same clinical and histopathological features.

Learning points

- ▶ Induced liver injury after high doses of methylprednisolone is rare.
- ▶ The mechanism of injury is unknown but it seems to be immune mediated.
- ▶ Drug-induced liver injury and autoimmune hepatitis may be difficult to differentiate, because of the similar clinical and histopathological features.
- ▶ Patients with multiple sclerosis taking high doses of methylprednisolone should be monitored.

Contributors ATO selected the clinical data and wrote the manuscript. MAC performed the histopathological evaluation of the liver biopsy. SL and CS participated on the literature review and in revising the manuscript.

Competing interests None declared.

Patient consent Obtained.

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